

**CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH**

SUMMARY OF TOXICOLOGY DATA

Triticonazole

**Chemical Code # 5799, Tolerance # 52891
SB 950 # NA**

Original: 5/29/02
Revised: 10/29/08

I. DATA GAP STATUS

Chronic toxicity, rat:	No data gap, no adverse effect
Chronic toxicity, dog:	No data gap, adverse effect indicated
Oncogenicity, rat:	No data gap, no adverse effect
Oncogenicity, mouse:	No data gap, no adverse effect
Reproduction, rat:	No data gap, no adverse effect
Teratology, rat:	No data gap, no adverse effect
Teratology, rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, no adverse effect
Chromosome effects:	No data gap, adverse effect indicated
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	No data gap, no adverse effect

Toxicology one-liners are attached.

All record numbers through 242057 were examined.

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

indicates a study on file but not yet reviewed.

File name: T081029

Thomas Moore, 5/29/02, revised 10/29/08

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

** 0053, 0098, 0115; 183736, 201451, 242057; "RPA400727: Combined Oncogenicity and Toxicity Study by Dietary Administration to CD Rats"; (P. Aughton; Pharmaco LSR Ltd, Eye, Suffolk, England; Report No. 94/RHA445/0134; 6/28/94); Fifty CD rats/sex/group were treated in the diet with 0, 5, 25, 750 or 5000 ppm of RPA 400727 (batch no. DA 646; purity: 97.1%) for 99 weeks (male) or 100 weeks (females) ((M) 0, 0.2, 1.0, 29.4, 203.6 mg/kg/day, (F) 0, 0.3, 1.3, 38.3, 286.6 mg/kg/day). An additional 15 animals/sex/group/time point were treated for 26 or 53 weeks and euthanized for interim histopathological evaluations. The mean weight gains for both sexes in the 5000 ppm group were less than those for the controls during the 1st week of treatment ($p < 0.01$) and up through 78 weeks for the males (NS) and 88 weeks for the females ($p < 0.01$). The mean body weights for the 5000 ppm treatment group were approximately 5% less for the males and 15% for the females than those of the control animals. There was no treatment-related effect upon food consumption. In the ophthalmology examination of the males, increased incidences of superficial opacity (0: 3/14 vs. 5000: 9/22) and superficial keratitis with vascularization of the cornea (0: 0/14 vs. 5000: 4/22) were apparent after 98 weeks of treatment. Atrophy of the iris was noted in the females of the high dose group (0: 2/22 vs. 5000: 8/30) after 98 weeks. Sclerosis of the lens (including nuclear sclerosis) was noted in the 5000 ppm males after 98 weeks (0: 2/14 vs. 5000: 10/22). At various times during the study, platelet counts were reduced in the 5000 ppm treatment group ((M), 24 and 76 weeks, $p < 0.05$), (F) 76 and 97 weeks, $p < 0.05$). Prothrombin times for the high dose females were increased at 76 and 97 weeks ($p < 0.01$). In the necropsy examination, there were no apparent effects upon organ weights. Among the non-neoplastic lesions noted, there was a slight increase in the incidence of diffuse hyperplasia in the zona reticularis of the adrenal gland in the high dose males at the termination of the study (0: 0/50 vs. 5000: 4/50). Increased incidence of focal medullary hyperplasia in the adrenal gland was likewise noted for these males at this time (0: 2/50 vs. 5000: 9/50). An increased incidence of multinucleated cells in the adrenal gland was noted for the high dose females at 26 (0: 0/15 vs. 5000: 9/15), 53 weeks (0: 0/15 vs. 5000: 3/14) and the termination of the study (0: 0/50 vs. 5000: 3/50). In the liver of the high dose females, there was an increased incidence of centriacinar hepatocytic vacuolation (0: 16/50 vs. 5000: 33/50, $p < 0.01$). Despite the increased incidence of ocular lesions noted for the 5000 ppm animals in the ophthalmology examination, the eyes of only a few of the animals in the various groups were examined histologically. For neoplastic lesions, although the males in the high dose group exhibited an increased incidence in pituitary adenomas at the termination of the study (0: 19/50, 5: 24/38, 25: 24/43, 750: 25/43, 5000: 29/50), there was no apparent dose response and the incidence at the high dose level was within the range for the historical control (36.7 to 60.0%). **No adverse effect indicated; Chronic Dietary NOEL:** (M/F) 750 ppm ((M) 29.4 mg/kg/day, (F) 38.3 mg/kg/day) (based upon the increased incidence of lesions in the liver and adrenal glands of both sexes in the 5000 ppm group); **No apparent oncogenicity.** Previously, the study was unacceptable, possibly upgradeable with the submission of historical control data for the incidence of ocular lesions. Additional information was submitted which delineated the historical control range for the various ocular effects noted in this study; the data indicate that either the incidence noted for a lesion in the 5000 ppm group was within the historical control range or that the control group of the opposite sex in this study suffered the lesion at even a higher rate than did the treated group for which a treatment-related effect had previously been noted. ; (Moore, 4/25/02, revised, Moore, 11/22/02, rerevised, 10/27/08)

CHRONIC TOXICITY, RAT

See the Combined Rat Study

CHRONIC TOXICITY, DOG

** 048; 183731; "RPA 400727: Toxicity Study by Oral (Capsule) Administration to Beagle Dogs for 52 Weeks"; (A. Broadmeadow; Pharmaco-LSR, Eye, Suffolk, England; Report No. 92/RHA441/0782; 2/10/93); Four beagle dogs/sex/group were treated by capsule with 0, 2.5, 25,

or 150 mg/kg/day of RPA 400727 (lot no.DA646, purity: 97.1%) for 12 months. One female in the 25 mg/kg treatment group was euthanized *in extremis* due to a non-treatment related reason. Body weight gain was decreased for both sexes in the 150 mg/kg group ($p<0.05$ or $p<0.001$). Mean overall food consumption was reduced in a dose-related manner for the females. In the periodic veterinary examinations, lenticular opacities and photophobia were noted after 25 weeks of treatment for the high dose group males. By 39 weeks, cataracts were present in the lenses of the eyes of both sexes of this group ((M) 0: 0/4, 150: 4/4, (F) 0: 0/4, 150: 3/4). These observations were confirmed in the ophthalmology examinations. In addition, the ophthalmology exam also revealed that the iris had irregular edges and a nodular appearance and/or the pupils only partially dilated ((M) 0: 0/4, 150: 3/4, (F) 0: 0/4, 150: 3/4). Thickened skin was first observed in two of the high dose males after 13 weeks of treatment. Erythema of the skin and the pinna was evident in 3 of the high dose males after 39 weeks of treatment. In the clinical chemistry, alkaline phosphatase (AP) activity was elevated after 12 weeks of treatment and thereafter for both sexes in the 150 mg/kg group ($p<0.001$). Although the 25 mg/kg females demonstrated increased AP activity as well, there was no histological evidence of injury in this group. Serum alanine amino transferase activity was elevated as well for the high dose group animals ($p<0.05$ or $p<0.01$). Total protein and albumin in the serum was decreased for both sexes in the 150 mg/kg group after 24 and 50 weeks of treatment. In the necropsy examination, the mean absolute and relative prostate weights of the 150 mg/kg group males were less than those of the controls ($p<0.05$). The mean absolute and relative testes weights of this group were greater than those of the controls ($p<0.05$). The mean relative adrenal, kidney, liver and thyroid weights for the high dose females were greater than those of the controls ($p<0.05$ or $p<0.01$). These effects were noted as a consequence of the high dose females having a lower mean body weight. Histological examination revealed vacuolation of the zona fascicularis in the adrenals (0: 1/8, 2.5: 1/8, 25: 3/7, 150: 7/8), lenticular degeneration of the eye (0: 0/8, 2.5: 0/8, 25: 0/7, 150: 7/8), focal inflammation associated with hepatocytic degeneration in the liver (0: 1/8, 2.5: 1/8, 25: 2/7, 150: 4/8) and acanthosis/hyperkeratosis of the skin (0: 0/8, 2.5: 0/8, 25: 0/8, 150: 5/8). **Possible adverse effect:** cataracts and lenticular degeneration in the eye; **NOEL:** (M/F) 25 mg/kg/day (based upon the effects upon body weight gain, serum enzymes and organ weights and histological lesions in the adrenals, eyes, liver and skin); **Study acceptable.** (Moore, 4/2/02)

ONCOGENICITY, RAT

See Rat Combined Study

ONCOGENICITY, MOUSE

** 054; 183737; "RPA 400727: Oncogenicity Study by Dietary Administration to CD-1 Mice for 78 Weeks"; (M. Eddie; Pharmaco-LSR Ltd, Eye, Suffolk, England; Report No. 93/RHA446/0778; 5/13/94); Sixty eight CD-1 mice/sex/group were treated in the diet with 0, 15, 150 or 1500 ppm of RPA 400727 (batch no. DA 646, purity: 97.1%) for up to 78 weeks. Sixteen animals/sex/group were designated for the interim sacrifice after 26 weeks of treatment. There was no treatment-related effect upon the survival of the animals. Mean body weight gain was less for the 1500 ppm group over the course of the study than that for the controls ($p<0.01$). Food consumption was not affected by the treatment. There was no treatment-related effect upon the hematology parameters. The target organ was the liver. The mean absolute and relative liver weights for both sexes of the 1500 ppm group were greater than those of the controls after 26 and 78 weeks of treatment ($p<0.05$ or $p<0.01$). An increased incidence of centriacinar hepatocytic large fatty vacuolation was noted for both sexes of the 1500 ppm group after 26 and 78 weeks of treatment ($p<0.05$, $p<0.01$ or $p<0.001$). **No adverse effect indicated. CHRONIC TOXICITY (M/F):** 150 ppm ((M): 17.4 mg/kg/day), (F): 20.1 mg/kg/day) (based upon the incidence of fatty vacuolation in the liver and increased mean absolute and relative liver weights observed for the 1500 ppm treatment group); **No oncogenicity observed. Study acceptable.** (Moore, 4/24/02)

REPRODUCTION, RAT

** 052; 183735; "Two-Generation Reproduction Study with RPA400727 in Rats"; (S.M. Henwood; Hazleton Wisconsin, Inc., Madison, WI; Project ID. HWI 6224-172; 1/13/93); Twenty eight Crl:CD BR rats/sex/group were treated in the diet with 0, 5, 25, 750 or 5000 ppm of RPA 400727 (lot no. DA646, purity: 97.1%) for two generations. The treatment included 10 weeks prior to mating,

mating, 3 weeks of gestation and 3 weeks of lactation. At that time, 28 F1 animals/sex/group were selected as parents and treated for a minimum of 10 weeks prior to mating, followed by mating and 3 weeks each of gestation and lactation of the F2 generation. The F1 males and F0 and F1 females in the 5000 ppm treatment group had a lower mean body weight than those of the controls at the end of the premating period and for the females during the gestation and lactation periods ($p < 0.01$). Mean food consumption was initially reduced during the first week for the F0 and F1 males and females in the 5000 ppm group ($p < 0.01$). This decreased food consumption persisted for the F1 males through the 10th week of premating ($p < 0.01$). In the histopathological evaluation, the adrenal glands of the 5000 ppm group in both generations exhibited cortical vacuolation (males, F0, 0: 7/28, 5000: 27/27, F1, 0: 15/28, 5: 9/28, 25: 8/28, 750: 9/28, 5000: 27/27 with increased severity), degeneration of cortical cells (females, F0, 0: 0/27, 5000: 22/24, F1, 0/28, 5000: 11/28) and presence of giant cells (females, F0, 0: 0/27, 5000: 16/24, F1, 0: 0/28, 5000: 14/28). A reduced number of F1 females in the 5000 ppm group were pregnant (0: 26/28 vs. 5000: 18/28). The mean litter size was reduced for the F1 5000 ppm group. Pup viability was reduced for the F1 generation in the 5000 ppm treatment group ($p < 0.01$). Mean pup weights for the 5000 ppm group of both generations were lower than those of the control over the course of the lactation period ($p < 0.01$). **No adverse effect indicated. Parental NOEL:** (M/F) 750 ppm (males: 45.1 to 48.1 mg/kg/day, females: 54.8 to 132.0 mg/kg/day) (based upon reduced mean body weight and lesions in the adrenal gland of the 5000 ppm treatment group), **Reproduction NOEL:** 750 ppm (54.8 to 132.0 mg/kg/day) (based upon the reduced number of pregnancies in the 5000 ppm group of the F1 parental generation), **Developmental NOEL:** 750 ppm (54.8 to 132.0 mg/kg/day) (based upon lower mean pup weights in the 5000 ppm group of both generations); **Study acceptable.** (Moore, 4/11/02)

TERATOLOGY, RAT

** 050; 183733; "RPA 400727: Teratology Study in the Rat"; (L.M. Burns; Life Science Research Limited, Eye, Suffolk, England; Report No. 90/RHA373/0189; 4/10/91); Twenty five mated CD female rats were dosed orally by gavage with 0, 40, 200 or 1000 mg/kg of RPA 400727 (lot no. YG2156/1, purity: 99.5%) from day 6 through day 15 of gestation. One female in the control group died on gestation day 8. The mean body weight gain for the 1000 mg/kg dams was less than that of the controls over gestation days 12 to 16 ($p < 0.05$). For the fetuses, there was an increased incidence of bilateral 14th ribs in the 1000 mg/kg treatment group (14.5 vs. 10.4% for the historical controls, concurrent control: 3/24 litters vs. 1000: 9/23 litters). Otherwise, there were no treatment-related effects upon the development of the fetuses. **No adverse effect indicated. Maternal NOEL:** 200 mg/kg (based upon reduced body weight gain for the dams in the 1000 mg/kg treatment group); **Developmental NOEL:** 200 mg/kg (based upon the increased incidence of bilateral 14th ribs in the fetuses of the 1000 mg/kg group); **Study acceptable.** (Moore, 4/3/02)

049; 183732; "RPA 400727: Preliminary Teratology Study in the Rat"; (C. Higgins; Life Science Research Limited, Eye, Suffolk, England; Report No. 90/RHA324/0428; 12/11/89); Six pregnant CD female rats/group were dosed orally by gavage with 0, 50, 250 or 1250 mg/kg/day of RPA 400727 (batch no. HU423, purity: 97.0%) from gestation days 6 through 15. Additional groups of pregnant females were dosed with LS840606. However, these study results were not pertinent to the present review. No deaths resulted from the treatment with RPA400727. Dams in the 1250 mg/kg group exhibited staining on the head, body and/or peri-genital area. The high dose animals exhibited a lower mean body weight than did the control animals by gestation day 16. There was an apparent treatment-related effect upon food consumption. The post implantation loss for the 1250 mg/kg females was greater than that of the controls and the mean fetal weight for this group was slightly less than that of the controls. An increased incidence of unilateral and bilateral hydronephrosis was noted in the kidneys of the high dose group fetuses. **No adverse effect indicated. Maternal NOEL:** 250 mg/kg (based upon lower mean body weight for the 1250 mg/kg females); **Developmental:** 250 mg/kg (based upon the incidence of hydronephrosis and increased post-implantation loss noted for the 1250 mg/kg fetuses); **Study supplemental** (non-guideline study). (Moore, 4/3/02)

TERATOLOGY, RABBIT

**** 051; 183734; "RPA 400727: Teratology Study in the Rabbit";** (L.M. Burns; Life Science Research Limited, Eye, Suffolk, England; Report No. 91/RHA428/0916; 11/28/91); Twenty artificially inseminated New Zealand White female rabbits/group were dosed by oral gavage with 0, 5, 25, 50 or 75 mg/kg/day with RPA 400727 (lot no. YG2156/1, purity: 99.5%) from day 6 through day 19 of gestation. Six of the 75 mg/kg group and 1 of the 50 mg/kg group were euthanized *in extremis* between days 13 and 17 of gestation. The mean body weight gain of the does in the 50 and 75 mg/kg/day groups between gestation days 6 and 8 was less than that of the control animals. There was a dose-related reduction in food consumption between days 6 and 12. The fetuses in the 75 mg/kg group demonstrated an increased incidence of various skeletal variations. Otherwise, no other treatment-related effects on development were evident. **No adverse effect indicated. Maternal NOEL:** 25 mg/kg/day (based upon reduced body weight gain and mortality for the 50 mg/kg/day treatment group); **Developmental NOEL:** 50 mg/kg/day (based upon increased incidence of skeletal variations for the fetuses in the 75 mg/kg/day treatment group); **Study acceptable.** (Moore, 4/5/02)

GENE MUTATION

**** 059; 183742; "RPA 400727: Investigation of Mutagenic Activity at the HGPRT Locus in a Chinese Hamster V79 Cell Mutation System";** (J.M. Lloyd; Life Sciences Research Limited, Eye, Suffolk, England; Report No. 91/RHA448/0742; 9/13/91); Chinese hamster V79 clone 6 cells were exposed to RPA 400727 (batch no. DA 646, purity: 97.1%) for 3 hours at 37° C at concentrations ranging from 62.5 to 1000 ug/ml with and w/o activation (based on the limit of solubility). Two trials were performed with duplicate samples per treatment level. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. Although some cultures demonstrated a marginal increase in mutation frequency, there was no evidence of a dose-response and the effects were not reproducible. There was no apparent treatment-related increase in the forward mutation rate. The positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 3/25/02)

CHROMOSOME EFFECTS

**** 057; 183740; "Triticonazole: Induction of Chromosome Aberrations in Cultured Human Peripheral Blood Lymphocytes";** (R. Marshall, Corning Hazleton (Europe), Harrogate, North Yorkshire HG3 1PY, England; Report No. 198/98-1052; 1/16/97); Human lymphocytes (whole blood) were treated with Triticonazole technical (batch no. OP 9550347, purity: 90.9%) at concentrations ranging from 7.751 to 800 ug/ml in the 1st trial (male) and 33.79 to 800 ug/ml in the 2nd trial (female) under conditions of activation and non-activation at 37° C. Under conditions of activation, the cells were exposed to the test material for 3 hours, washed and then incubated for an additional 17 hours (1st trial) and 17 or 41 hours (2nd trial). In the non-activated assays, the cells were exposed to the test material for 20 hours (1st trial) and 20 or 44 hours (2nd trial). A liver homogenate S9 fraction from male rats pretreated with Aroclor 1254 was used to metabolize the test material. In the first trial, an increase in cells with aberrations was noted in a dose-related manner at the two higher treatment levels evaluated ($p < 0.01$ and $p < 0.001$) under conditions of non-activation. The majority of the aberrations were chromosomal or chromatid deletions. This increase in the number of cells with aberrations was not as evident in the 2nd trial for the cells incubated for 20 hours. For the one treatment level evaluated after exposure to the test material for 44 hours without activation, the number of cells with aberrations was increased ($p < 0.05$). Metabolism of the test material did not apparently result in an increased number of cells with chromosomal aberrations. The results of the assay were suggestive of a positive response without activation. The results indicate that the test material is possibly genotoxic. **Indicated adverse effect:** increased numbers of cells with chromosomal aberrations without activation. The positive controls were functional for both activation and non-activation. **Study acceptable.** (Moore, 3/22/02)

DNA DAMAGE

**** 058; 183741; "RPA 400727: Induction of Unscheduled DNA Synthesis (UDS) in Rat Hepatocytes *In Vitro*";** (B. Foster; Life Sciences Research Limited, Eye, Suffolk, England; Report No. 92/RHA466/0351; 5/21/92); Primary rat hepatocyte cultures were exposed to RPA 400727 (batch no. DA 646, purity: 97.1%) at concentrations ranging from 7.81 to 125 ug/ml for 18 hours at

37° C. There were 3 cultures per treatment level. However, only two of the cultures were evaluated for unscheduled DNA synthesis (UDS). There was no treatment-related increase in UDS. The positive control was functional. **No adverse effect indicated. Study acceptable.** (Moore, 3/22/02)

** 060; 183743; "RPA 400727: Assessment of Clastogenic Action on Bone Marrow Erythrocytes in the Micronucleus Test"; (C.N. Edwards; Life Sciences Research Limited, Eye, Suffolk, England; Report No. 92/RHA470/0315; 5/21/92); Fifteen CD-1 mice/sex/group were dosed orally by gavage with 0 (0.5% aqueous methyl cellulose) or 625 mg/kg of RPA 400727 (batch no. DA 646, purity: 97.1%). Five animals/sex/group/time point were euthanized at 24, 48 and 72 hours post-dose. In addition, 5 animals/sex/group were dosed with 25 and 125 mg/kg of the test material and 30 mg/kg of chlorambucil (positive control) and euthanized at 24 hours post-dose. Bone marrow samples from the femurs of each animal were examined and the number of polychromatic erythrocytes (PCE) with a micronucleus was determined. The ratio of PCE's to mature erythrocytes was calculated as well. There was no treatment-related increase in the number of PCE's with a micronucleus. **No adverse effect indicated.** The positive control was functional. **Study acceptable.** (Moore, 3/26/02)

NEUROTOXICITY

52891-046; 183729; "Benchmark and Time-to-Peak Effect Neurotoxicity Study with Triticonazole in Rats"; (M.S. Weiler; Corning Hazleton Inc., Madison, Wisconsin; Project ID. CHW 6224-226; 3/7/97); Four Crl:CD (SD)BR VAF/Plus rats/sex/group were dosed orally with 0 (0.5% aqueous methyl cellulose), 50, 1000 or 2000 mg/kg of Triticonazole (lot no. 9550347, purity: 97.2%). An additional 8 males were treated with 2000 mg/kg of the test material. An abbreviated Functional Observational Battery (FOB) and a motor activity assessment were performed at 2 hours post-dose for the first four groups. For the second 2000 mg/kg group, 4 animals each were examined at 1 and 4 hours post-dose. There was no treatment-related effect upon any of the FOB parameters. In the motor activity assessment, the treated animals demonstrated a dose-related increase in total counts with a maximal number of counts noted at 2 hours post-dose. **No adverse effect indicated. Supplemental Study** (non-guideline study). (Moore, 4/24/02)

52891-042; 183725; "Acute Neurotoxicity Study with Triticonazole in Rats"; (M.S. Weiler; Corning Hazleton Inc., Madison, Wisconsin; Project ID CHW 6224-227; 7/14/97); Ten Crl:CD (SD)BR VAF/Plus rats/sex/group were dosed orally by gavage with 80, 400 or 2000 mg/kg of Triticonazole (lot no. 9550347, purity: 97.2%). FOB and motor activity measurements were conducted predose, and at 2 hours and 7 and 14 days after treatment. Histopathological examination of nerve tissue from whole-body perfused animals was undertaken. There were no treatment-related clinical signs, body weight gain, FOB or motor activity measurements. There were no treatment-related lesions. **No adverse effect indicated. ACUTE NEUROTOXICITY NOEL:** (M/F) > 2000 mg/kg; **Study acceptable.** (Moore, 3/22/02)

52891-047; 183730; "13-Week Dietary Neurotoxicity Study with Triticonazole in Rats"; (M.S. Weiler; Corning Hazleton Inc., Madison, Wisconsin; Project ID. CHW 6224-228; 7/14/97); Ten Crl:CD (SD) BR VAF/Plus rats/sex/group were treated in the diet with 0, 500, 2500 or 10000 ppm of Triticonazole (lot no. 9550347, purity: 97.2%) for 13 weeks ((M): 0, 32.5, 170, 695 mg/kg/day, (F) 0, 38.5, 199, 820 mg/kg/day). Functional observational battery and motor activity assessments were performed after 4, 8 and 13 weeks of treatment. Histopathological examination of nerve tissue from whole-body perfused animals was performed. No deaths resulted from the treatment. During the initial week of the treatment, the 10000 ppm animals demonstrated decreased mean body weight gain for both sexes ($p < 0.05$). This decrease in weight gain was based upon diminished food consumption for that week ($p < 0.05$). Thereafter, both body weight gain and food consumption were similar for both the control and high dose groups. There were no treatment-related effects upon clinical signs and FOB and motor activity measurements. No treatment-related lesions were noted in the histopathology examination. **No adverse effect indicated. Subchronic Neurotoxicity NOEL:** (M/F) > 10000 ppm ((M): > 695 mg/kg/day, (F) > 820 mg/kg/day) (based upon the lack of treatment-related effects at the highest dose tested); **Study acceptable.** (Moore, 4/23/02)

SUBCHRONIC STUDIES

52891-044; 183727; "RPA400727: Toxicity Study by Dietary Administration to CD Rats for 13 Weeks"; (P. Aughton; Life Science Research Limited, Eye, Suffolk, England; Report No. 91/RHA429/0793; 12/10/91); Ten CD rats/sex/group were treated in the diet with 0, 25, 250, 12500 or 25000 ppm of RPA 400727 (batch nos. YG 2156/1 (purity: 98.9%), YG 2160/1 (purity: 98.2%) for 13 weeks ((M) 0, 1.1, 11.7, 674, 1437 mg/kg/day, (F) 0, 1.4, 13.3, 829, 1686 mg/kg/day). One female in the 250 ppm group was euthanized *in extremis*. The death, due to renal failure, was not treatment-related,. The mean body weight gains for the 12500 and 25000 ppm treatment groups were less than that of the control ($p < 0.01$). Food consumption was reduced for these two groups, especially during the first weeks of the study. Hematocrit and hemoglobin content were lower for both sexes in the 25000 ppm group than those for the control ($p < 0.01$). MCV and MCH were both reduced for the females in the 12500 and 25000 groups. Total white blood cell and lymphocyte counts were increased for the 25000 ppm females. The total cholesterol in the serum was increased for both sexes at 12500 and 25000 ppm. Although the mean absolute organ weights for numerous organs of the high dose group were less than those of the control (adrenals (F only), heart, kidneys (M only), lungs, spleen (M only), thymus, and uterus), this was largely due to the lower mean body weight of the high dose animals overall. The mean absolute and relative liver weights for the 12500 and 25000 ppm females and the relative liver weights for the 12500 and 25000 ppm males were greater than those of the control ($p < 0.01$). The relative kidney and ovary weights for the 12500 and 25000 ppm females were greater than those of the controls ($p < 0.01$). The mean relative testes weights for the 12500 and 25000 ppm males were greater than those of the controls ($p < 0.01$). The two target organs were the adrenals and liver. For the males, cortical fatty vacuolation of the adrenals was the primary lesion (0: 1/10, 25: 4/10, 250: 8/10, 12500: 10/10, 25000: 10/10). For the females, cortical fatty vacuolation (0: 0/10, 250: 1/9, 12500: 4/10, 25000: 10/10) and degeneration of the zona reticularis (0: 0/10, 12500: 9/10, 25000: 10/10) were the primary lesions in the adrenals. In the liver, there was a treatment-related increase in periportal hepatocytic hypertrophy of both sexes ((M), 0: 0/10, 250: 2/10, 12500: 6/10, 25000: 10/10, (F) 0: 0/10, 12500: 6/10, 25000: 9/10). Centriportal hepatocytic fatty vacuolation was noted for the 12500 and 25000 ppm females (0: 3/10, 12500: 7/10, 25000: 10/10). **No adverse effect indicated. NOEL:** (M) <25 ppm (<1.1 mg/kg/day) (based upon the increased incidence of cortical fatty vacuolation in the adrenals of the 25 ppm treatment group males (not statistically significant); (F) 250 ppm (13.3 mg/kg/day) (based upon increased incidence of lesions in the adrenals and liver of the 12500 ppm treatment group); **Study acceptable.** (Moore, 4/12/02)

52891-043; 183726; "RPA 400727: Preliminary Toxicity Study by Dietary Administration to F-344 Rats for Four Weeks"; (P. Aughton; Life Sciences Research Limited, Eye, Suffolk, England; Report No. 90/RHA359/0947; 2/26/91); Five F-344 rats/sex/group received 0, 500, 1500, 5000, 15000 or 50000 ppm of RPA 400727 (lot no. YG2156/1, purity: 99.5%) for 4 weeks in the diet ((M) 0, 50.12, 152.3, 513.2, 1494, 4802 mg/kg/day, (F) 0, 52.44, 151.3, 489.4, 1476, 4945 mg/kg/day). There were no deaths during the study. Treatment-related clinical signs included thin appearance for both sexes in the 50000 ppm treatment group and hunched posture for the females in the 50000 ppm group. Mean body weight gain for the 5000 ppm treatment group and above during the first 4 days of dosing was less than that of the control ($p < 0.001$). The effect on body weight gain persisted for the males of these groups through the remainder of the study ($p < 0.001$). Only the females in the 50000 ppm group demonstrated reduced body weight gain throughout the study ($p < 0.01$ or $p < 0.001$). Mean food consumption was reduced for both sexes in the 5000 ppm group and above. In the hematology, the mean hemoglobin, the mean hematocrit and the mean corpuscular hemoglobin levels were reduced for both sexes in the 50000 ppm treatment group ($p < 0.001$ or $p < 0.05$). Likewise, the mean total white blood cell counts were reduced for both sexes in the 50000 ppm group ($p < 0.001$ or $p < 0.05$) and for the females in the 15000 ppm group ($p < 0.001$) with reduced numbers of neutrophils and lymphocytes accounting for the differences. Platelet counts were reduced for the 5000 ppm and above males and for the 15000 ppm females and above. Mean alkaline phosphatase activity was increased for the 15000 and 50000 ppm females ($p < 0.001$). The mean total cholesterol levels were increased for the 5000 and 15000 ppm males and for the 1500, 5000 and 15000 ppm females ($p < 0.001$). Ketones were identified in

the urinalysis of both sexes in the 50000 ppm group. Although most of the mean organ weights were lower than those of the controls due to the reduced weight gain demonstrated by the higher dose animals, certain of the organs exhibited apparent treatment-related changes in weight. The mean absolute and relative liver weights for the 5000 ppm females and above and the mean relative liver weights for the 15000 ppm males and above were increased above those of the control ($p < 0.01$). The mean absolute thymus weights were lower for both sexes in the 50000 ppm group ($p < 0.01$). The mean relative thyroid weights for the 15000 and 50000 ppm males were greater than that of the control ($p < 0.05$ or $p < 0.01$). The mean absolute prostate weights for the 5000 ppm males and above were reduced from that of the controls ($p < 0.05$ or $p < 0.01$). The mean relative prostate weight for the 50000 ppm group was likewise less than that of the control ($p < 0.01$). The mean relative testes weights for the 5000 ppm males and above were greater than that of the control ($p < 0.01$). The mean absolute testes weight for the 50000 ppm males was less than that of the control ($p < 0.01$). However, no lesions in the prostate or testes noted in the histological examination. The mean absolute uterine plus cervix weights were reduced for all groups of females 1500 ppm and above ($p < 0.05$ or $p < 0.01$). The relative uterine weight was lower than that of the control for the 5000 ($p < 0.05$) and 50000 ppm treatment groups ($p < 0.01$). In the liver, there was an increased incidence of panacinar microvacuolation and centriacinar hepatocytic fatty vacuolation for the 50000 ppm males (0: 0/5, 50000: 5/5, for both lesions) and for the 15000 ppm and 50000 ppm females (0:0/5, 15000: 5/5, 50000: 3/5 (microvacuolation), 0:0/5, 15000: 3/5, 50000: 1/5 (centriacinar fatty vacuolation). Hepatocyte hypertrophy was also noted for the 50000 ppm females (0: 0/5, 50000: 4/5). In the uterus, there was an increased incidence of reduced endometrial stroma for the females in the 15000 and 50000 ppm treatment groups (0: 0/5, 15000: 2/5, 50000: 5/5). **Possible adverse effect indicated:** treatment-related effect upon the reproductive tissues. **NOEL:** (M) 1500 ppm ((M) 152.3 mg/kg/day) (based upon reduced body weight gain and effects on prostate and testes weights in the 5000 ppm group males, (F) 1500 ppm (151.3 mg/kg/day) (based upon lower relative uterine weight and increased liver weight for the 5000 ppm females); **Supplemental Study** (non-guideline study). (Moore, 3/28/02)

52891-045; 183728; "3-Week Dermal Toxicity Study with Triciconazole in Rats"; (M.S. Weiler; Corning Hazleton Inc., Madison, Wisconsin; Project ID. CHW 6224-229; 7/14/97); Five CrI:CD (SD)BR VAF/Plus rats/sex/group were treated by repeated dermal application for 6 to 7 hours per day for 23 days with 0, 100, 300, or 1000 mg/kg/day of Triciconazole (lot no. 9550347, purity: 97.2%). The test material was moistened with reverse osmosis water at the time of application to ensure adequate contact with the skin. One female in the 1000 mg/kg group died on day 17. The death was not considered to be treatment-related. No treatment-related effects upon food consumption or incidence of dermal irritation were evident. No treatment-related effects upon the hematology and clinical chemistry parameters were noted. In the necropsy examination, there were no treatment-related effects upon organ weights. No treatment-related lesions were noted in the histopathological examination. **No adverse effect indicated. Dermal Systemic NOEL:** (M/F) > 1000 mg/kg/day (based upon the lack of treatment-related effects in the highest dose tested); **Study acceptable.** (Moore, 4/24/02)